

Transient microstructural brain anomalies and epileptiform discharges in mice defective for epilepsy and language-related NMDA receptor subunit gene *Grin2a*

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Abstract

Wiley Periodicals, Inc. © 2018 International League Against Epilepsy Objective: The epilepsy-aphasia spectrum (EAS) is a heterogeneous group of age-dependent childhood disorders characterized by sleep-activated discharges associated with infrequent seizures and language, cognitive, and behavioral deficits. Defects in the *GRIN2A* gene, encoding a subunit of glutamate-gated N-methyl-D-aspartate (NMDA) receptors, represent the most important cause of EAS identified so far. Neocortical or thalamic lesions were detected in a subset of severe EAS disorders, and more subtle anomalies were reported in patients with so-called “benign” phenotypes. However, whether brain structural alterations exist in the context of *GRIN2A* defects is unknown. Methods: Magnetic resonance diffusion tensor imaging (MR-DTI) was used to perform longitudinal analysis of the brain at 3 developmental timepoints in living mice genetically knocked out (KO) for *Grin2a*. In addition, electroencephalography (EEG) was recorded using multisite extracellular electrodes to characterize the neocortical activity in vivo. Results: Microstructural alterations were detected in the neocortex, the corpus callosum, the hippocampus, and the thalamus of *Grin2a* KO mice. Most MR-DTI alterations were detected at a specific developmental stage when mice were aged 30 days, but not at earlier (15 days) or later (2 months) ages. EEG analysis detected epileptiform discharges in *Grin2a* KO mice in the third postnatal week. Significance: *Grin2a* KO mice replicated several anomalies found in patients with EAS disorders. Transient structural alterations detected by MR-DTI recalled the age-dependent course of EAS disorders, which in humans start during childhood and show variable outcome at the onset of adolescence. Together with the epileptiform discharges detected in young *Grin2a* KO mice, our data suggested the existence of early anomalies in the maturation of the neocortical and thalamocortical systems. Whereas the possible relationship of those anomalies with sleep warrants further investigations, our data suggest that *Grin2a* KO mice may serve as an animal model to study the neuronal mechanisms of EAS disorders and to design new therapeutic strategies.

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Keywords

brain structure, EEG, epilepsy-aphasia, mouse model, MR-DTI

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